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EXAMINER	
ZISKA, S	

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

07/24/96

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 2/2/95 & 10/11/95

☐ This action is **FINAL**. 11/21/97

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three (3) month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-17, 25-36 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-17, 25-36 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

This application should be reviewed for errors.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The declaration of Dr. Reynolds is acknowledged, has been considered and is addressed, below.

Claims 1-17 and 25-35 are active and examined in this Office Action. Claims 18-24 have been cancelled.

The provisional rejection of claims 1-17 and 25-35 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of copending application serial no. 08/010,829 in view of Cepko is maintained. Applicants have not argued the rejection.

The rejection of claims 1-17 under 35 U.S.C. 101 is withdrawn. Applicants' arguments are moot.

The rejection of claims 1-17 and 35 under 35 U.S.C. 112, first paragraph, regarding the "associating" is withdrawn.

The rejection of claims 1-17 and 25-35 under 35 U.S.C. 112, first paragraph, regarding the isolation of neural stem cells from a tissue of a donor is maintained. Applicants' arguments, filed October 11, 1995, have been considered but not found to be persuasive. Applicants have argued that the term "isolated" is not meant to imply that a pure population of stem cells is obtained. However, the claim language should be amended to reflect the idea that the tissue is dissociated to obtain a population of neural cells comprising neural stem cells. Regarding applicant's further arguments, it is not possible to dissociate only stem cells from a donor tissue, either as known from the art or as taught in the specification.

The rejection of claims 25-28 and 30 under 35 U.S.C. 102(b) as being anticipated by Hunter is maintained. Applicants' arguments, filed October 11, 1995, have been considered but not found to be persuasive. Applicants have argued that Hunter does

not teach production of glial cells from a neural stem cell since Hunter does not teach clonal derivation. However, such arguments are not persuasive since claim 25 is a method claim but does not claim clonal proliferation of a single cell. Applicants' arguments from pages 6-8 are not commensurate with the method as claimed.

Applicants have, on page 9 of the amendment, stated that stem cells obtained from neural tissue remain quiescent in the culture conditions of Hunter and Bottenstein and that, in other words, the culture conditions of Hunter and Bottenstein do not induce stem cell proliferation since no neurosphere formation was shown. However, the claim does not require clonal proliferation or neurosphere formation; applicant's arguments are not commensurate with the claimed method.

Claim 36 is rejected under 35 U.S.C. § 103 as being unpatentable over Hunter as applied to claims 25-28 and 30 above and further in view of Almazan. Claims 25-28 and 30 were rejected under 35 U.S.C. 102(b) for reasons as stated above. Almazan discloses maintaining the fetal brain cells in a serum-free chemically defined medium for 12-25 days in culture and further that EGF was added to the culture later at days 2 and 5. It would have been obvious to one of ordinary skill to modify the method of Hunter by substituting the defined medium containing the growth factor in view of the teachings of Almazan that the cells would differentiate under those experimental conditions.

The rejection of claim 29 under 35 U.S.C. 103 as being unpatentable over Hunter as applied to claims 25-28 and 30 above and further in view of Morrison is maintained. Applicants' arguments above for claims 25-28 and 30, regarding the lack of proliferation of the neural stem cells have been repeated herein. However, the claim does not require clonal proliferation or

neurosphere formation; applicant's arguments are not commensurate with the claimed method.

The rejection of claims 1, 3-6 and 35 under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Gage and Masters is maintained. Applicants have argued that the method of Hunter does not result in proliferation; that the claimed methods require the proliferation of multipotent stem cells in the presence of a growth factor; that Boyles merely teaches that glial cells and neurons are sources of apolipoproteins, proteins known to be necessary in the process of remyelination; and that in any case, neither the Masters, nor Hunter and Bottenstein references disclose the proliferation of neural stem cells. However, contrary to such arguments, claim 1 claims dissociation of a tissue containing neural stem cells and harvesting of precursor cells while Hunter and Masters teaches the proliferation of neural cells obtained from a tissue clearly having stem cells. Hunter and Masters started with brain tissue and neither removed the "neural stem cells" from the cell culture.

Applicants have argued that Gage does not teach transplantation of autologous neural stem cells. However, Gage clearly suggests the use of "replicating embryonic neural cells" for purposes of transplantation in column 12, further, the brain is known as an immunologically privileged site and the use of "autologous" does not provide a patentable distinction.

Applicants have directed the examiner's attention to the New York Times article, demonstrating the belief at the time that researchers did not believe that neural stem cells existed in the adult mammalian CNS. However, the claims are not limited to the adult CNS; the examiner appreciates the importance of the invention but points out that the claimed invention is not commensurate with the arguments presented. No claim claims adult

CNS; no claim claims cells produced by clonal proliferation from a single cell. The examiner suggests inserting the limitation of claim 4 into claim 1, for example.

Regarding arguments directed to the presence of nestin-expressing cells in the neurosphere, applicants have speculated that the examiner may infer that the cells of the neurosphere are not clonally derived. Such is not the case; the expression of nestin merely indicates that not all the cells in the neurosphere are either stem cells or progenitor cells but that the cells in the neurosphere represent both undifferentiated progeny stem cells and differentiated stem cell progeny. Applicants again point out that the claimed methods differ from those of Hunter but applicants are reminded that the claims do not claim clonal derivation or neurospheres.

The rejection of claims 2 under 35 U.S.C. 103 as being unpatentable over Boyles, taken with Hunter, Masters, Gage as applied to claims 1, 3-6 and 35 and further in view of Morrison is maintained.

Applicants have argued at the middle/bottom of page 14 that EGF is the growth factor required by claim 2 and that claim 2 includes all the limitations of claim 1. The examiner does not disagree. Claim 1 requires the proliferation of neural stem cells to produce precursor cells and therefore implies differentiation of the daughter stem cell to another cell type, usually a precursor cell destined to achieve a different cellular fate. Perhaps one miscommunicated point is the definition of precursor cells. A precursor cell is not the same as a progeny daughter stem cell. The proliferation of neural stem cells is the replication of neural stem cells to produce other neural stem cells. Part (b) of claim 1, when using the word "proliferating" in order to obtain precursor cells, must also include the process of differentiating. The examiner disagrees with applicant's

assessment of the teachings of Morrison; Morrison used a primary culture of brain cells, known to contain stem cells.

The rejection of claims 7, 8, 10-13 and 15-17 under 35 U.S.C. 103 as being unpatentable over Boyles taken with Hunter, Masters and Gage is maintained.

Applicants have argued that the examiner has erred in the statement that claims 15-17 do not required transplantation. However, the examiner has considered that claim 15-17 are in vitro, as the phrase "associating the oligodendrocytes with a demyelinated axon to effect remyelination" does not have the in vivo limitation. Contacting may occur in a petri dish, as applicants have previously pointed out. In claim 7, there is no positive recitation of reimplantation of the cells back into the recipient. In claim 15, the demyelinated axons in the petri dish may be those of an intended recipient, the method of claim 7 useful for in vitro studies of the interaction. Claims 16 and 17 do not add the intended in vivo limitation.

The examiner understands that a dependent claim includes all the limitations of the independent claim; the independent-dependent claim relationship is not the issue. Applicants' arguments are not commensurate with the claimed invention. Note that the in vivo claims, claims 18-24 were non-elected in paper 4, the restriction requirement dividing the claims into in vivo and in vitro methods.

Applicants have argued that the examiner's obviousness rejection is based on selectively picking and choosing various features of the cited references without looking at what the references teach as a whole. Applicants have stated that the examiner has argued that "Hunter was not cited to teach stimulation of proliferation using EGF". The examiner originally cited Morrison with respect to the use of EGF. Hunter used EGF with oligodendrocyte/astrocyte precursor cells and the abstract

states that EGF inhibited the action of B104CM (conditioned medium). Applicants have argued that the examiner cannot ignore the teaching of the Hunter reference that EGF does not induce the proliferation of undifferentiated cells. However, the examiner cited Morrison to teach the ability of EGF to stimulate the proliferation and differentiation of glial cells. The examiner does not dispute the Hunter was unable to detect growth; however, perhaps it was some other factor in the B104CM which rendered EGF inactive or use of EGF at subeffective levels. Morrison clearly discloses that positive effect of EGF on glial cell growth. Morrison addresses the issue of EGF in the presence of conditioned medium. Morrison discloses in table 2, that EGF in the presence of CM was less effective in promoting growth than EGF alone. Therefore, the inability of Hunter to show proliferation was, in light of the teachings of Morrison, most likely due to the presence of CM.

The rejection of claim 14 under 35 U.S.C. 103 as being unpatentable over Boyles, Hunter, Gage and Masters as applied to claims 7, 8, 10-13 and 15-17 above and further in view of Freshney is maintained. Applicants have argued that none of the references cited by the examiner disclose a method for the proliferation of neural stem cells. However, contrary to such arguments, the art is correctly applied to the method as claimed because the claims do not simply claim proliferation of neural stem cells. The claims claim a method of proliferating to produce precursor cells which involves differentiation of the produced progeny.

The rejection of claims 31-34 under 35 U.S.C. 103 as being unpatentable over Hunter or Almazan taken with Freshney is maintained. Applicants have argued the Hunter or Almazan references alone and not in combination with Freshney. Freshney was cited to disclose cloning by serial dilution to obtain a

population of cells derived from a single cell and thereby teaches the methods by which clonally derived neurospheres may be obtained.

The declaration of Dr. Reynolds is acknowledged, has been considered and is insufficient to overcome the rejection. Dr. Reynolds argues that Hunter only showed proliferation of O-2A progenitor cells and not proliferation of neural stem cells. Dr. Reynolds further compares his methods with those of Hunter and discloses that Hunter failed to obtain clusters of cells and concludes that the method of Hunter did not induce the neural stem cells to proliferate. However, claim 1, for example, requires the proliferation of stem cells to produce precursor cells and Hunter shows that production of precursor cells from a population of cells containing the neural stem cell. Claim 1 does not require the use of clonally derived neurospheres, which is the method used by declarant. The declaration is not commensurate with the scope of the claims.

No claim is allowed. The application contains patentable subject matter but the claims are not commensurate with what applicants argue is the invention.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO FAX center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Suzanne Ziska, Ph.D., whose telephone number is (703)308-1217. In the event the examiner is not available, the examiner's supervisor, Ms. Jacqueline Stone, may be contacted at phone number (703) 308-3153.

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800